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May 14, 2009

DRUG INFORMATION

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Dear Mr. Citron:

Thank you for discussing AGGRENOX® capsules (aspirin/extended-release dipyridamole 25mg/200mg) with your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Joseph Riedl. You requested information regarding the following topic(s):

• AMCP Dossier
• The PRoFESS Trial

If you did not request this information, please contact our Drug Information Unit Call Center at 1-800-542-6257 (option #4).

AGGRENOX is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Thank you for your interest in AGGRENOX capsules. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

The Drug Information Unit Healthcare Professional Staff

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AGHIAS/2009-013182

AMCP Dossier

The AMCP dossier is intended to provide clinical and outcome data that are useful for formulary review. The Drug Information Unit is available to answer questions regarding the content of this material. Please contact your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Joseph Riedl for the scheduling of consultations.

The PRoFESS Trial

The PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial was a multicenter, randomized, double-dummy, double-blind active and placebo controlled trial designed to compare the fixed combination of low-dose (25 mg) aspirin (ASA) and (ER DP) extended release dipyridamole (200 mg) given twice daily with clopidogrel (75 mg) tablets given once daily for recurrent stroke prevention. Also, in a second simultaneous randomization, (80mg) of Micardis® (telmisartan) was given once daily, and compared to placebo on the same endpoint. The trial utilized a 2 x 2 factorial design in a large, diverse patient population (n = 20,332), involving 695 centers from 35 countries.[1] PRoFESS was initially designed to compare the efficacy and safety of ASA + ER DP with the combination of clopidogrel plus aspirin; however the study design was amended early after the MATCH trial showed that adding ASA to clopidogrel in patients presenting with transient ischemic attack or minor stroke provided little additional benefit, but significantly increased the bleeding risk.[1, 2, 3] The 2027 patients initially allocated to the clopidogrel + ASA group had been treated for up to 8 months, before they were switched to clopidogrel alone at the time of the amendment. The remaining 18,305 patients were subsequently randomized to ASA + ER DP or clopidogrel alone.[3]

The primary outcome of the PRoFESS trial was the time to first recurrent stroke over the course of the study, using a time-to-event analysis. The most important secondary outcome was the composite of stroke, myocardial infarction or vascular death. Additional secondary outcomes include the aforementioned composite plus congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, transient ischemic attack, cerebral venous thrombosis or retinal vascular accident not classified as stroke), any death, stroke subtype by Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria and Mini Mental State Examination score. The risk of major hemorrhagic events was assessed during the safety evaluation.[1]

Inclusion and Exclusion criteria:

Patients included in PRoFESS were individuals who were ≥ 55 years old, and who had had an ischemic stroke within 90 days of entry to the study. The study also included patients aged 50–54 years and/or 91–120 days after the qualifying stroke provided the patient had two of the following additional risk factors: diabetes mellitus, hypertension, smoker at time of qualifying stroke, obesity (BMI > 30), previous vascular disease (stroke, MI, or peripheral arterial disease), end-organ damage (retinopathy, left ventricular hypertrophy, or microalbuminuria), or hyperlipidemia. Further, eligible patients had to be clinically and neurologically stable prior to being randomized, and not deteriorating or having a progressive stroke or other condition. The diagnosis of the ischemic stroke was based on the investigator's clinical judgment, and supplemented with evidence on a CT scan or other imaging modality, such as MRI of the brain. Positive evidence on brain imaging was not required to diagnose stroke if symptoms lasted greater than 24 hours, but brain imaging which confirmed the presence of a new brain infarct consistent with the clinical syndrome was required if symptoms lasted less than 24 hours. Eligible patients who had stents were also allowed to enroll in PRoFESS, however, patients who have undergone a carotid endarterectomy were excluded. Some other exclusion criteria preventing patients from being enrolled in the study were: presenting with a primary hemorrhagic stroke, known brain tumor, pre-stroke history of dementia requiring institutional care, a modified Rankin scale score > 4 at baseline, a patient who was unlikely to be released from the hospital following the qualifying stroke, uncontrolled hypertension, and known severe renal insufficiency or severe hepatic dysfunction. For a more complete listing of all PRoFESS trial inclusion and exclusion criteria, please refer to reference number one.[1]

Baseline Characteristics:

Table 1 shows the baseline characteristics for the study population entering the PRoFESS trial. The average age of patients entering the study was 66.1 ± 8.6 years, and 36% were females. Almost 25% of the PRoFESS patients had a history of stroke or TIA prior to the index stroke; 47% had hyperlipidemia, 74% were hypertensive, 28% were diabetic, and 16% had ischemic coronary artery disease. Within 10 days from the qualifying event, 39.9% of patients were randomized into the study, and 15 days was the median time to randomization. The qualifying events of patients enrolled in PRoFESS according to the TOAST criteria were: 28.5% of strokes due to large artery atherosclerosis, 52.1% to small-vessel disease (lacune), 1.8% to cardioembolism, 2.0% to other determined etiologies, and 15.5% were strokes of undetermined etiology. The four most commonly used concomitant medications at randomization

were statins (47.2%), ACE inhibitors (36.8%), calcium channel blockers (24.2%) and beta-blockers (20.7%). The mean blood pressure at randomization was 144/84 mmHg, and the mean BMI was 26.8. The median score of the first Mini Mental State Examination administered during the study was 28, measured 30 days post baseline.[1, 3]

Table 1: Baseline Patient Demographics for PRoFESS[1]

Total patients	**20,332**
Mean age, years	66.1
Gender, % female	36.0
Race or ethnic group (%)	
South Asian	8.4
Chinese	18.0
Japanese	1.1
Malay	0.6
Other Asian	4.6
Arab, Persian	0.2
Black African, African Americans	4.0
European, Caucasian	57.3
Native Latin	4.5
Caribbean Hispanic	0.3
Other	0.8
Median time from qualifying event to randomization, days	15
Time groups, %	
≤10 days	39.9
11-30 days	29.0
≥ 31 days	31.1
Medications at baseline (%)	
ACE inhibitors	36.8
ARBs	5.2
Beta-blockers	20.7
Loop active diuretics	3.2
Thiazide diuretics	17.1
Potassium-sparing diuretics	1.5
Calcium channel blockers	24.2
Statins	47.2
Fibrates	1.
Insulin	5.6
Oral hypoglycemics	18.6
Risk factors, %	
Current smoker	21.2
Former smoker	36.2
Regular alcohol consumption (>1 drink per week)	35.4

Physical examination (mean)	
BP mmHg	144/84
BMI	26.8
Waist circumference, cm	96.5
Modified Rankin scale, %	
Score 0	14.1
Score 1	37.3
Score 2	25.0
Score 3-5	23.7
TOAST classification, %	
Large-artery atherosclerosis	28.5
Cardioembolism	1.8
Small-artery occlusion (lacune)	52.1
Acute stroke of other etiology	2.0
Stroke of undetermined etiology	15.5
Median MMSE (Mini Mental State Examination)	28
MMSE groups, %	
Score < 25	17.4
25-27	21.1
28	13.3
29	19.1
30	29.1
Medical history, %	
Previous stroke (prior to qualifying stroke)	18.3
TIA	8.6
MI	6.7
CHF	2.6
PAOD	2.9
Hypertension	73.8
Diabetes mellitus	28.1
Hyperlipidemia	46.6
Ischemic coronary artery disease	16.2
Atrial fibrillation	2.6
Valvular disease	1.7
Deep venous thrombosis	1.5

TIA = Transient ischemic attack
CHF = congestive heart failure
PAOD = peripheral arterial obstructive disease
CCB = calcium channel blocker; BP = blood pressure BMI = body mass index

MMSE = Mini Mental State Examination

Study Design and Treatment Schedule:

Patients who had consented to participate in PRoFESS, and who met the entry criteria were randomized in a double-blind fashion to receive either ASA + ER DP (25 mg/200 mg twice daily) or clopidogrel (75 mg once daily) as well as either telmisartan (80 mg once daily) or placebo as shown in the figure below.[1]

PRoFESS Trial Design.[1]

	ASA + ER DP	**Clopidogrel**
Telmisartan	ASA + ER DP + Telmisartan (n=5000)	Clopidogrel + Telmisartan (n=5000)
Placebo	ASA + ER DP + Placebo (n=5000)	Clopidogrel + Placebo (n=5000)

All patients were treated for hypertension, if necessary, using standard open-label blood pressure medications permitted by the study protocol. Patients were informed as to which analgesic medications were permitted, and investigating physicians were encouraged to control blood pressure based on current guidelines for blood pressure control, and to manage other risk factors. A diuretic would be the first recommended blood pressure-lowering drug to be added if necessary, followed by a beta-blocker, or a calcium channel blocker. Angiotensin receptor antagonists were not allowed in PRoFESS, but the addition of ACE inhibitors was permitted. Other restricted medications included anticoagulants (excluding short-term use of anticoagulants), ASA-containing medication, other platelet inhibitors, thrombolytic agents and glycoprotein IIb/IIIa inhibitors. Also, special instructions were provided to investigators for managing patients with headache, to reduce the amount of patients discontinuing the study medication due to this adverse event.[1]

Patients could be randomized while still in the hospital following the qualifying stroke, depending upon qualifications and risk factors, or up to 120 days following the stroke. Patients were evaluated at hospital discharge, or after one week, whichever came first, and again at 1 month, 3 months and 6 months. For the remainder of the study, clinic visits were scheduled every 6 months, with a telephone contact scheduled approximately halfway between each visit.[1]

An independent Data Monitoring Committee regularly monitored the results of the trial. When approximately one third and two thirds of stroke outcome events occurred, two interim efficacy analyses were performed. An independent adjudication and assessment committee verified all primary and key secondary outcomes blinded to treatment allocation. At least 2 adjudicators reviewed all strokes, as well as most other adjudicated events according to established protocols and procedures. If a randomized patient suffered a stroke, the TOAST criteria were used to classify the stroke as soon as possible after the event. To assess the degree of disability, the modified Rankin scale assessment was repeated three months after the secondary stroke, and the Barthel activities of daily living index was administered.[1]

PRoFESS Efficacy Results:

The primary outcome was time to first recurrent stroke with a pre-specified non-inferiority margin. Across an average observation time of 2.5 years, the primary outcome of first recurrent stroke occurred in 916 patients (9.0%) in the ASA + ER DP group and 898 patients (8.8%) in the clopidogrel group [hazard ratio (HR) 1.01, 95% CI 0.92-1.11]. The hazard ratio was very close to 1.0 (equivalence) between the two antiplatelet regimens, but since the upper

limit of the 95% CI exceeded the protocol-specified non-inferiority margin of 1.075; therefore, formal statistical non-inferiority of ASA + ER DP vs. clopidogrel could not be established.[3, 4]

Across multiple pre-specified and exploratory baseline subgroups, the relative difference between ASA + ER DP and clopidogrel for the primary outcome of first recurrent stroke was also consistent.[3] For the on-treatment analysis of the primary outcome, the results were [ASA + ER DP 777 (7.7%) recurrent strokes vs. clopidogrel 777 (7.7%); HR 1.07, 95% CI 0.97-1.18]. [3]

In further exploratory analyses of the main secondary endpoint of the composite of stroke, myocardial infarction or vascular death, ASA + ER DP and clopidogrel showed similar outcomes [(n=1333), 13.1% ASA + ER DP, vs. (n=1333), 13.1% clopidogrel; HR 0.99, 95% CI 0.92-1.07, p=0.83].[3, 4]

The rates of most tertiary efficacy outcomes were similar with the two agents, although the rate of new or worsening congestive heart failure was significantly lower in the ASA + ER DP group compared to clopidogrel [144 (1.4%) vs. 182 (1.8%); HR 0.78, 95% CI 0.62-0.96].[3]

As stated above, other regimens in PRoFESS investigated whether telmisartan, combined with ASA + ER DP or clopidogrel, would further reduce the risk of recurrent stroke. Initiation of blood pressure lowering with telmisartan after a stroke, with a relatively short duration of therapy of 2.5 years, did not significantly lower the rate of stroke or other major vascular events compared to placebo, according to results from PRoFESS. There was no significant difference in the number of patients with stroke in the telmisartan group compared to the placebo group (8.7% vs. 9.2%, respectively; hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.86-1.04, p=0.23). Thus, the primary endpoint of superiority of telmisartan versus placebo could not be statistically confirmed. The mean follow-up period was 2.5 years, and it is unclear whether a longer follow-up period would have yielded statistical significance.[4]

Exploratory analyses with telmisartan suggested that there was no difference in the rates of recurrent stroke or major vascular events in the first 6 months of the trial (number of strokes: telmisartan 3.4% vs. placebo 3.2%; HR 1.07, 95% CI 0.92-1.25, p=0.38; major vascular events: telmisartan 4.7% vs. placebo 4.3%; HR 1.10, 95% CI 0.97-1.26, p=0.14). However, beyond 6 months the number of events were lower in the telmisartan group (number of strokes: telmisartan 5.3% vs. placebo 6.0%; HR 0.88, 95% CI 0.78-0.99, p=0.029; major vascular events: telmisartan 8.8% vs. placebo 10.1%; HR 0.87, CI 0.80-0.95, p=0.0029).[4]

Also, there was no significant reduction in two secondary telmisartan arm outcomes: 1) major vascular events (cardiovascular death, myocardial infarction, stroke and new or worsening heart failure) with telmisartan compared to placebo (13.5% vs. 14.4%, respectively; HR 0.94, 95% CI 0.87-1.01, p=0.11) or 2) rate of new diabetes mellitus (125 in the telmisartan group and 151 in the placebo group; HR 0.82, 95% CI 0.65 to 1.04, p=0.10).[4]

As stated above, functional outcome after a recurrent stroke was evaluated during PRoFESS using the modified Rankin scale, and the Barthel index 3 months after the stroke. The PRoFESS results showed that the functional outcome of recurrent stroke is similar in patients who receive ASA + ER DP compared with clopidogrel, or telmisartan compared with placebo. There was also no difference between these treatment groups for cognitive function in patients with recurrent stroke. Similar results were observed with the Barthel Index for all the treatment groups. Also, no difference was observed among the treatment groups with respect to the proportion of patients who were cognitively impaired (Mini Mental State Examination $\leq$24). Overall, approximately 18%, 14%, and 15% were cognitively impaired at 1 month, 2 years, and at the next to last study visit, respectively.[4]

Safety Results:

In PRoFESS, recurrent ischemic strokes occurred in 7.7% of patients in the ASA + ER DP group compared to 7.9 % in the clopidogrel group. Although there were 25 fewer ischemic stroke recurrences in the ASA + ER DP group compared to clopidogrel, 5 more other/unknown strokes and 38 more hemorrhagic strokes were found in the ASA + ER DP group.[3, 4]

Despite the greater number of hemorrhagic strokes in the ASA + ER DP group, the number of individuals with fatal or disabling strokes (defined by a modified Rankin scale ≥ 3 at 3-months post-recurrent stroke) was similar in the two groups with 413 (4.1%) in the ASA + ER DP group, and 392 (3.9%) in the clopidogrel group [HR 1.05, 95% CI 0.96-1.16].[3]

Major hemorrhagic events occurred more frequently in the ASA + ER DP group (major hemorrhagic events: (419, 4.1%) compared to clopidogrel alone (365, 3.6%); HR 1.15, 95% CI 1.00-1.32, p=0.06). [3, 4]

Intracranial hemorrhages were a subset of major hemorrhagic events. The overall incidence of intracranial hemorrhage (including the 128 hemorrhagic strokes counted in the primary outcome) was higher in the ASA + ER DP group (1.4%) than in the clopidogrel group (1.0%) resulting in a HR of 1.42 (95% CI 1.11, 1.83, p=0.006). The difference between the treatment groups resulted mainly from the higher incidence of hemorrhagic strokes in the ASA + ER DP group.[3, 4]

The benefit-risk ratio expressed as the rate of recurrent stroke or major hemorrhagic event was not significantly different between ASA + ER DP and clopidogrel [ASA + ER DP 1194 (11.7%) vs. clopidogrel 1156 (11.4%); HR 1.03, 95% CI 0.95-1.11, p=0.50]. The total number of deaths in the study were 739 (7.3%) in the ASA + ER DP group, and 756 (7.4%) for clopidogrel.[3, 4]

The ASA + ER DP group had significantly more frequent premature discontinuations from study drug (2961, 29%), compared to clopidogrel (2290, 23%; p<0.001). Also, the ASA + ER DP group had a higher rate of adverse events leading to permanent discontinuation of study drug compared to clopidogrel [1650 (16.4%) vs. 1069 (10.6%)]. Further, permanent discontinuation from the ASA + ER DP group, because of headache was more common (593, 5.9%) compared to clopidogrel (87, 0.9%).[3]

In summary, the PRoFESS trial did not meet the pre-defined criteria for non-inferiority, but demonstrated similar rates of recurrent strokes with ASA + ER DP and clopidogrel. PRoFESS shows no evidence that either ASA + ER DP or clopidogrel was superior to the other in prevention of recurrent stroke.[3]

References:

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3. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359:1238-1251.
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5. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1-13.